PROPOSAL TO THE COUNCIL
FOR TOBACCO RESEARCH FOR
SUPPORT OF A GORDON RESEARCH
CONFERENCE ON ELASTIN

I. Amount requested from the Council for Tobacco Research: $2,500.

II. Proposed Duration: August 15, 1983 - August 19, 1983.

III. PIs: Robert Rucker, Ph.D[redacted]
Department of Nutrition
University of California
Davis, CA 95616

Herbert Kagen
Department of Biochemistry
Boston University
School of Medicine
Boston, MA

IV. Authorized Organization Representative:

Alexander M. Cruickshank
Gordon Research Conference
Pastore Chemical Laboratory
University of Rhode Island
Lower College Road
Kingston, RI 02881

Summer Address:
Colby-Sawyer College
New London, NH 03257

V. Abstract:

The overall purpose of this conference is to provide a forum for the exchange of ideas, information, and techniques in areas of importance to the study of elastin function, structure, and metabolism. The topics chosen for the 1983 Gordon Research Conference focus on 1) improving our understanding of elastin's role in biology and pathobiology and 2) improving our understanding of the complexities of elastin chemistry and structure. For example, it is now clear that key features of lung and vascular tissue development are related to events that are dependent upon synthesis and accumulation of elastin. Chronic obstructive lung and atherosclerosis have as major components in their respective sequelae defects in elastin fiber integrity. Thus, emphasis is given to elastin gene expression and its controls as well as to the importance of elastin in lung and vascular injury. Attention will also be given to elastin's role as an elastomer and to events important to the post-translational modification (enzymatic and chemical) of elastin. As in the past, it is anticipated that the proposed meeting will bring together basic scientists from a variety of disciplines, because of the novel chemical features of elastin and its importance to major diseases in man.

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VI. Fund Use:

Reimbursement for foreign and domestic travel by participants. We will follow the rules for dispersing travel funds to invited speakers and discussants given in the guidelines of the Gordon Research Conferences. The guidelines allow reimbursement for registration fees, subsistence at the conference site, and travel to and from the conference location (economy or coach fare). No allowances will be given to non-conferees. In addition, no allowance will be made for car rentals nor will any honorarium be paid to anyone at the conference.

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PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
RUCKER, Robert B.	Professor	3/29/41

EDUCATION (*Begin with baccalaureate training and include postdoctoral*)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Oklahoma City University, Oklahoma	B.S.	1963	Chemistry
Purdue University, Lafayette, Indiana	M.S.	1966	Biochemistry
Purdue University, Lafayette, Indiana	Ph.D.	1968	Biochemistry

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

Professional Positions: Post-doctoral experience - September 1968 to September 1970 - University of Missouri; research in the area of connective tissue metabolism.
From January 1978 to present have held a joint appointment in Biological Chemistry (40%), School of Medicine, University of California, Davis.
From September 1970 to present, have held the positions of Assistant, Associate or Full Professor and Chairman in the Department of Nutrition, University of California, Davis.

Memberships: American Association for the Advancement of Science; Sigma Xi; American Institute of Nutrition; American Chemistry Society; Society for Experimental Biology and Medicine; Orthopaedic Research Society.

Publications (since 1980 to early 1982):

1. Rucker, R.B., M. Dubick and J. Robinson. Hypothetical calculations of ascorbic acid synthesis in vivo. American Journal of Clinical Nutrition 33:961-964, 1980.

2. Lefevre, M. and R.B. Rucker. Elastin turnover in hypercholesterolemic and normal Japanese quail. Biochimica et Biophysica Acta 630:519-526, 1980.

3. Rucker, R.B. and M. Lefevre. Chemical changes in elastin as a function of maturation In: Chemical degradation of proteins (Ed. J. Whitaker and M. Fujimaki). American Chemical Society Symposium Series 123: 63-82, American Chemical Society Press, Washington, D.C., 1980.

4. Lin, H-J, D.R. Benson, R.S. Riggins, R.B. Rucker and U.K. Abbott. Plasma-free hydroxproline, growth, and sexual maturity in the scoliotic chicken. Proceedings of the Society for Experimental Biology and Medicine 165:345-348, 1980.

5. Hodges, R.E., R.B. Rucker and R.H. Gardner. Vitamin A deficiency and abnormal metabolism of iron. Ann. New York Academy of Sciences 355:58-61, 1980.

6. Leach, R.M., R.B. Rucker and G.P. Van Dyke. Eggshell membrane protein: A non-elastin desmoine/isodesmoine containing protein. Archives of Biochemistry Biophysics 207: 353-359, 1981.

7. Dubick, M.A., R.B. Rucker, J.A. Last, L.O. Lollini, C.E. Cross. Elastin turnover in murine lung after repeated exposure to ozone. Journal of Applied Toxicology Pharmacology 58:203-210, 1981.

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8. Buckingham, K., C.S. Khoo, M. Dubick, M. Lefevre, C.E. Cross, L. Julian and R.B. Rucker. Copper deficiency and elastin metablism in avian lung. Proceedings of the Society for Experimental Biology 166:310-319, 1981.

9. Dubick, M., R.B. Rucker, C.E. Cross, J.A. Last. Elastin metabolism in rodent lung. Biochimica et Biophysica Acta 672:303-306, 1981.

10. Rucker, R.B. and M. Dubick. Response to Ginter's letter. American Journal of Clinical Nutrition 34:1450-1451, 1981.

11. Cutler, A.D., R.S. Riggins, H.-J. Lin, D. Benson, M.R. Ramey, L.R. Herrman, R.B. Rucker and U.K. Abbott. Stress relaxation in connective tissue of chickens with scoliosis. Journal of Biomechanics 14:439-442, 1981.

12. Valentine, R., W. Riemann, G. Fisher and R.B. Rucker. An elastase inhibitor from isolated bovine pulmonary macrophages. Proceedings of the Society for Experimental Biology and Medicine 168:238-244, 1981.

13. Smith, D.W., L.B. Sandberg, B.H. Leslie, T.B. Wolf, S.T. Minton, B. Meyers and R.B. Rucker. Primary structure of a chick tropoelastin peptide: Evidence for a collagen-like amino acid sequence. Biochemical and Biophysical Research Communications 103:880-885, 1981.

14. Rucker, R.B. Isolation of soluble elastin from copper-deficient chick aorta. Methods of Enzymology 82:650-657, 1982.

15. Opsahl, W., M. Ellison, S.H. Zeronian, D. Lewis, R.S. Riggins and R.B. Rucker. Role of copper in collagen crosslinking and its influence on selected mechanical properties of chick bone and tendon. Journal of Nutrition 112:708-716, 1982.

16. Lefevre, M., H. Heng and R.B. Rucker. Dietary cadium, zinc, and copper: Effects on chick lung morphology and elastin crosslinking. Journal of Nutrition 112:1344-1352, 1982.

17. Keen, C.L., B. Lonnerdal, M. Clegg, L.S. Hurley, J. Morris, R. Rogers and R.B. Rucker. Developmental changes in composition of cat milk: Trace elements, minerals, protein, carbohydrates and fat. Journal of Nutrition 112: , 1982.

18. Meyers, B.A., M.A. Dubick, R.B. Rucker, A.C. Jackson, K.M. Reiger, S.M. Williams and J.A. Last. Nutritional effects on lung connective tissue. I. Protein-deficient rats. Journal of Applied Physiological, 1982, in press.

19. Dubick, M.A., J.A. Last, C.E. Cross and R.B. Rucker. Interactions of ascorbic acid supplementation and bleomycin instillation on murine lung connective tissue metabolism. Drug-Nutrient Interactions, 1982, in press.

20. Lefevre, M. and R.B. Rucker. Modification of arterial elastin in vivo: Effects of age and diet on changes in the N-terminal amino acid content of aorta elastin. Biochimica Biophysica Acta, 1982, in press.

21. Dubick, M.A., J.W. Critchfield, J.A. Last, C.E. Cross and R.B. Rucker. Ascorbic acid turnover in the mouse following acute ozone exposure. Toxicology, in press, 1982.

22. Rucker, R.B. and M. Dubick. Lung elastin metabolism. In: Lung Toxicology-Target Organ Toxicology Monograph Series, ed., G.E.R. Hook, Raven Press, New York, 1982, in press.

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BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator. Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Herbert M. Kagan	Professor of Biochemistry	August 18, 1932

EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Massachusetts, Amherst, MA	B.S.	1954	Bacteriology
University of Massachusetts, Amherst, MA	M.S.	1956	Bacteriology
Tufts University, Medford, MA	Ph.D.	1966	Biochemistry

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

1966-69 Research Fellow, American Cancer Society, Department of Biological Chemistry, Harvard Medical School

1969-70 Assistant Research Professor, Department of Biochemistry, Boston University School of Medicine

1970-72 Assistant Professor, Department of Biochemistry, Boston University School of Medicine

1972-80 Associate Professor, Department of Biochemistry, Boston University School of Medicine

1980- Professor, Department of Biochemistry, Boston University School of Medicine.

Areas of Expertise:

Enzymology and protein chemistry of connective tissue; chemistry of elastin, properties of lysyl oxidase; role of connective tissue proteins in atherosclerosis and emphysema; histochemistry of elastase.

Selected Publications since 1974 - 1981:

Foster, J.A., Hewitt, N.A., Lewis, W., Kagan, H.M. and Franzblau, C. Isolation and characterization of crosslinked peptides from elastin. J. Biol. Chem. 249, 6191-6196 (1974).

Jordan, R., Hewitt, N.A., Lewis, W., Kagan, H.M. and Franzblau, C. Regulation of elastase-catalyzed hydrolysis of insoluble elastin by synthetic and naturally occurring hydrophobic ligands. Biochemistry 13, 3497-3503 (1974).

Snider, G.L., Hayes, J.A., Franzblau, C., Kagan, H.M., Stone, P.S. and Korthy, A.S. Relationship between elastolytic activity and experimental emphysema-inducing properties of papain preparations. Amer. Rev. Respir. Dis. 110, 254-262 (1974).

Kagan, H.M., Hewitt, N.A., Salcedo, L.L. and Franzblau, C. Catalytic activity of aort lysyl oxidase in an insoluble enzyme-substrate complex. Biochim. Biophys. Acta 365, 223-234 (1974).

Mukherjee, D.P., Kagan, H.M., Jordan, R.E. and Franzblau, C. Effect of hydrophobic elastin ligands on the stress-strain properties of elastin fibers. Conn. Tiss. Res. 4, 177-179 (1976).

Kagan, H.M. and Lerch, R.M. Amidated carboxyl groups in elastin. Biochim. Biophys. Acta 434, 223-232 (1976).

Kagan, H.M., Jordan, R.E., Lerch, R.M., Mukherjee, D.P., Stone, P. and Franzblau, C. Factors affecting the proteolytic degradation of elastin. Adv. Exp. Biol. Med. 79 189-207 (1977).

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Jordan, R.E., Milbury, P., Sullivan, K.A., Trackman, P.C. and Kagan, H.M. Studies on lysyl oxidase of bovine ligamentum nuchae and bovine aorta. Adv. Exp. Biol. Med. 531-540 (1977).

Stone, P., Pereira, W., Jr., Biles, D., Snider, G.L., Kagan, H.M. and Franzblau C. Studies on the fate of pancreatic elastase in the hamster lung. ^{14}C-guanidinated elastase. Amer. Rev. Respir. Dis.116, 49-56 (1977).

Stone, P., Kagan, H.M., Faris, B. and Franzblau, C. The kinetics of elastolysis as a probe of elastin. Anal. Biochem. 80, 597-600 (1977).

Kagan, H.M., Milbury, P.E., Jr., and Kramsch, D.M. A possible role for elastin ligand in the proteolytic degradation of arterial elastic lamellae. Cir. Res. 44, 95-103 (1979).

Kagan, H.M., Sullivan, K.A., Olsson, T.A. and Cronlund, A.L. Purification and propert of four species of lysyl oxidase from bovine aorta. Biochm. J. 177, 203-214 (1979)

Kagan, H.M. Changes in the state of ionization of carboxyl groups in elastin in respo to the binding of sodium dodecyl sulfate. Conn. Tiss. Res. 6, 167-169 (1979).

Madia, A.M., Rozovski, S.J. and Kagan, H.M. Changes in lung lysyl oxidase activity in streptozotocin-diabetes and starvation. Biochim. Biophys. Acta 585, 481-487 (1979

Trackman, P.C. and Kagan, H.M. Non-peptidyl amine inhibitors are substrates of lysyl oxidase. J. Biol. Chem. 254, 7831-7836 (1979).

Clark, J.M., Aiken, B.M. and Kagan, H.M. Ultrastructural localization of elastase-lik enzymes. J. Histochem. Cytochem. 28, 90-92 (1980).

Clark, J.M., Vaughan, D.W., Aiken, B.M. and Kagan, H.M. Elastase-like enzymes in huma neutrophils localized by ultrastructural cytochemistry. J. Cell Biol. 84, 102-119 (1980).

Brody, J., Kagan, H.M. and Manalo, A. Lung lysyl oxidase activity: relation to lung growth. Amer. Rev. Respir. Dis. 120,1289-1304 (1979.

Kagan, H.M., Tseng, L., Trackman, P.C., Okamoto, K., Rapaka, R.S. and Urry, D.W. Repe polypetpide models of elastin as substrates for lysyl oxidase. J. Biol. Chem. 255 3656-3659 (1980).

Kagan, H.M., Tseng, L. and Simpson, D.E. Control of elastin metabolism by elastin ligands: reciprocal effects of lysyl oxidase activity. J. Biol. Chem. 256, 5417-5421 (1981).

Kagan, H.M., Simpson, D.E. and Tseng, L. Substrate-directed modulation of elastin oxidation by lysyl oxidase. Conn. Tiss. Res. 8, 213-217 (1981).

Trackman, P.E., Zoski, C.G. and Kagan, H.M. Development of a peroxidase-coupled fluorometric assay for lysyl oxidase. Anal. Biochem., in press, 1981.

Kagan, H.M. and Sullivan, K.A. Purification and properties of lysyl oxidase. its rol in elastin biosynthesis. Methods in Enzymology, Contractile and Structural Protei In press, 1981.

Stone, P.J., Franzblau, C. and Kagan, H.M. Proteolysis of insoluble elastin. Methods in Enzymology, Contractile and Structural Protein. In press, 1981.

Kagan, H.M., Raghavan, J. and Hollander, W. Changes in aortic lysyl oxidase activity in diet-induced atherosclerosis in the rabbit. Arteriosclerosis. In press, 1981.

Chichester, C.O., Palmer, K.C., Hayes, J.A. and Kagan, H.M. Lung lysyl oxidase and prolyl hydroxylase: increases induced by cadmium chloride inhalation and the effe of 3-aminopropionitrile. Amer. Rev. Respir. Dis., in review, 1981.

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A. INTRODUCTION (Aims and Significance)

1. Objective. The proposed conference will provide a forum for the critical exchange of ideas, information and expertise in areas important to the understanding of elastin. As an area of investigation there has recently been an increase in concepts and information as well as in the number and diversity of investigators. This conference will serve to provide visibility to the importance of elastin and will create a forum in which scientists can interact and influence each other.

The Gordon Conference approach which has been so successful in other fields for over 3 decades, is ideally suited for this purpose. Its format, duration and location provide the opportunity for an intensive mingling of ideas and exchange of information by new and old workers from diverse disciplines. It is anticipated (based on the experience of the prior two Gordon Conferences on elastin) that these interactions will stimulate further progress in the field.

2. Background. Within the past 10 years there has been a substantial increase in the amount and scope of work on elastin. There has been a large influx of new workers from many disciplines. These events make apparent the need for a conference to facilitate discussion and interaction. In addition, a need for informal presentation of novel notions and the opportunity for a critical forum for new information and approaches are always essential for areas that have broad application. These conditions led to the first two Gordon Conferences on elastin which were held in 1979 and 1981. They were outstanding successes. Approximately 100 scientists attended each of the two conferences. For the conference in 1981, there were 23 foreign conferees (out of 97). Approximately 20 percent of the conferees were from industry or government. At the last conference, the conferees' evaluation indicated that the conference was warmly received and appreciated. Very favorable comments were received regarding the scientific content, the quality of the discussion, the general atmosphere and management of the meeting. The present objective is to continue this forum with another conference in 1983 that will at least equal or exceed the success of the first two conferences.

That elastin is worthy to be singled out for a conference is based in part on the following. First, elastin is one of the most novel of mammalian structural proteins. It 1) serves as an elastomer, 2) is more apolar than most proteins secreted from mammalian cells, 3) is expressed or synthesized predominantly during well-defined periods in organogenesis, 4) is not substantially degraded once synthesized, but 5) is subject to considerable posttranslational modification (enzymatic and chemical). Thus, to the physical protein chemist the protein serves as a model to test thermodynamic theories on elasticity. Since elastin contains long extensible chains composed of neutral amino acids that are crosslinked together by lysyl-derived crosslinks, it provides an unusual model from which to gather information on protein structure. The observations that crosslinked elastin normally does not undergo significant catabolism following synthesis dictates that control on elastin synthesis at the level of transcription and translation be particularly precise. Indeed work dealing with the regulatory features of the elastin gene will be a very visible part of this conference.

Elastin is also important to several disease states, such as atherosclerosis and emphysema; thus there is considerable interest in elastin, because elastin appears to be a factor in these diseases. Attention will be given to elastin's role in lung development in addition to repair and injury processes. Further, chemotatic properties of elastin peptides will be

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discussed. The interaction of elastin with cells and other macromolecules within the intracellular matrix will represent another major theme.

These topics were chosen on the basis of detailed responses from scientists in the field and also reflect ideas discussed at the last Gordon Conference. The topics represent areas that are felt to be currently important and areas undergoing rapid increase in knowledge. Informal communication between workers in the field is urgently needed to maintain momentum, sharpen issues and make projections for the future.

B. SPECIFIC OBJECTIVES AND METHODS

The third conference on elastin has received the approval and financial support of the Gordon Research Conference authorities. The conference will be held the week of August 15-19, 1983 at Kimball Union Academy, Meriden, New Hampshire. At the last Gordon Conference, Drs. Robert Rucker and Herbert Kagan were elected by the conferees to be Chairman and Vice-Chairman respectively of the 1983 conference. The conference will be operated according to the format and under the rules of the Gordon Research Conference. This is a long-established organization with an outstanding history of successful scientific conferences.

A tentative agenda has been selected. It was developed by the Chairman with input from leading scientists in the area. Thus far, response to invitations have been enthusiastic, but there will be the need for travel funds.

The topics chosen for the 1983 Gordon Research Conference on elastin focus on improving our understanding of the biochemistry as well as the pathobiology of elastin-related processes. We have attempted to identify specific areas which are unusually worthy of discussion. The topics chosen are outlined in the following tentative program.

Although the overall theme of the conference is broad, past experience has demonstrated that some diversification has attracted a variety of scientists with both basic and clinical interests. The program is designed to maximize discussion. The amount of time spent in prepared presentations will be approximately half f the allotted time. Also, we will attempt to maximize presentation and discussion of new advances and minimize review of already published material. Discussion is off-the-record and will emphasize the analysis of important problems and opportunities. There will also be the possibility of a poster session(s) and/or posted reprints to facilitate exchange between the scientists present. We hope to be able to attract not only leaders in the field of elastin biochemistry, but others in allied areas that would benefit from a better understanding of the protein as well as contribute their concerns and expertise. Consequently, we will publicize the Conference widely (journals, such as Science, Nature, Connective Tissue Research, etc.) and do our best to insure that those selected to attend will make major contributions to the Conference. We hope that the Conference will reflect the frontier and cutting edge of elastin biochemistry. The following details the tentative program for the proposed 1983 Gordon Research Conference. It is again emphasized, however, that this program is subject to some changes. New advances in the cloning of elastin or related genes will undoubtedly cause some modification of the Tuesday morning and/or evening program. The Principal Investigator has also asked each of the principal discussion leaders to identify potential participants from industry to augment or comment in their sections as discussants.

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ELASTIN

GORDON CONFERENCE

PROGRAM OUTLINE

KIMBALL UNION ACADEMY

Robert B. Rucker, Chairperson, Herbert Kagen, Vice Chairperson

15 August: Physical properties and chemical structure of elastin and tropoelastin (Dan W. Urry, Discussion Leader), L. B. Sandberg, James E. Mark, John Gosline; speakers. Post-translational modification of tropoelastin (Herbert Kagan, Discussion Leader), E. Harris, B. Starcher, R.B. Rucker; speakers.

16 August: Structure and function of the elastin gene (Jeff Davidson, Discussion Leader), Celeste Rich, J. Rosenbloom; Charles Boyd; speakers. Factors that modify elastin gene expression (Joel Rosenbloom, Discussion Leader), Zena Werb, David Wrenn, C.Franzblau; speakers.

17 August: Chemotactic properties of elastin and the interaction of elastin with cells and other macromolecules (Robert Mecham and Robert Senior, Discussion Leaders), Brian Toole; speaker. Components and structure of the elastic matrix (Judy Foster, Discussion Leader), Barbara Streeten, Theodore Cleary, Steven Karr; speakers.

18 August: Elastolytic proteinases: Their properties, sources and interactions (Zena Werb and James Travis, Discussion Leaders), Michael Banda, James H. McKerrow, James Powers, Raymond McDonald, John Sundsmo, Kazuyuki Morihara; speakers. Role of Elastin in lung growth, lung development and lung disease (Jerome Brody and Charles Kuhn, Discussion Leaders), V. Ranga, Gerald Turino; speakers.

19 August: Involvement of elastin in vascular tissue atherosclerosis, skin and inherited diseases (Carl Franzblau and Jouni Uitto, Discussion Leaders), Andrea J. Perejda, Aarne Oikarinen, William Hollander, Leslie Robert; speakers.

In addition to the program, participants may also submit posters on the topics indicated. Applicants should include a title and brief abstract of an anticipated poster presentation with their application.

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